Residential Insecticide Use and Risk of Non-Hodgkin's Lymphoma

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Abstract

Previous studies have linked non-Hodgkin's lymphoma (NHL) with occupational exposure to insecticides, but residential use is largely unexplored. In this population-based case-control study, we examined NHL risk and use of insecticides in the home and garden. We identified NHL cases, uninfected with HIV, diagnosed between 1998 and 2000 among women and men ages 20 to 74 years in Iowa and the metropolitan areas of Los Angeles, Detroit, and Seattle. Controls were selected using random digit dialing or Medicare files. Computer-assisted personal interviews (1,321 cases and 1,057 controls) elicited data on insecticide use at each home occupied since 1970. Insecticide levels were measured in dust taken from used vacuum cleaner bags (682 cases and 513 controls). We previously reported a positive association with dichlorodiphenyldichloroethylene levels in carpet dust residues. Here, we focus on insecticides that were commonly used after 1970, the time period covered by our questionnaire. People whose homes were treated for termites had elevated NHL risk (odds ratio, 1.3; 95% confidence interval, 1.0-1.6). Risk was modestly, although not significantly, elevated in all but one study center and in all sexes and races. The elevation in risk was restricted to people whose homes were treated before the 1988 chlordane ban. There was a significant trend of increasing risk with increasing levels of α-chlordane residues in dust (P_{trend} = 0.04) and a marginally significant trend for γ-chlordane (P_{trend} = 0.06). We found no evidence of associations for insects overall, for specific types of insects other than termites, or for elevated residues of other insecticides. We concluded that chlordane treatment of homes for termites may increase residents' NHL risk. (Cancer Epidemiol Biomarkers Prev 2006;15(2):251–7)

Introduction

Insecticides are biologically active chemicals, and several studies have linked occupational use of insecticides with elevated non-Hodgkin's lymphoma (NHL) risk. The effect of residential insecticide use on NHL risk is largely unexplored, despite the fact that insecticides are used in the homes or gardens of most American households (1). Therefore, we conducted a multicenter, population-based case-control study to examine residential insecticide use and NHL risk. We used a novel approach for assessing historical exposure to insecticides, combining detailed information from an in-person interview with measurements of insecticide residues in carpet dust samples. Some insecticides applied indoors or tracked in from outside persist in carpet dust for months or years, where they are largely protected from degradation by sunlight, rain, temperature extremes, and microbial action (2).

We focus here on insecticides that were widely used in peoples' homes and yards between 1970 and 2000, the time frame covered by our questionnaire. We do not include dichlorodiphenyltrichloroethylene (DDT) because it was banned in the United States in 1972. However, in a previous analysis of organochlorine compounds in carpet dust, we reported a positive association between dust residues of dichlorodiphenyldichloroethylene (DDE) (a metabolite of DDT) and NHL risk (3).

Materials and Methods

Study Subject Selection and Data Collection. This study was conducted in four areas covered by the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute: Iowa, Los Angeles County, and the metropolitan areas of Detroit and Seattle. Eligible cases were men and women ages 20 to 74 years, newly diagnosed with a first primary NHL between July 1998 and June 2000 and uninfected with HIV. We stratified case selection on center and race to maximize the number of African Americans. All consecutive cases (mostly Caucasian) were selected in Iowa and Seattle; all African-American cases and a random sample of Caucasian cases were selected in Detroit and Los Angeles. Controls were selected from the general population, frequency matched to cases on age, sex, race, and center. Controls under age 65 were identified by random digit dialing, and those 65 and older were identified from Medicare files. Pathology reports were classified according to the *International Classification of Diseases for Oncology*, 3rd Edition (morphology codes 967-972) as coded by the Surveillance, Epidemiology, and End Results registries. The study was approved by human subjects review boards at all institutions.

Subjects were mailed a residential and occupational history calendar and a self-administered questionnaire (diet or family medical history). During the subsequent home visit, the interviewer administered a computer-assisted personal interview and collected a blood or saliva sample, a carpet dust

Received 7/27/05; revised 11/16/05; accepted 12/15/05.

Grant support: National Cancer Institute Contracts N01-PC-67009 (S. Davis), N01-PC-65064 (R.K. Severson), N01-CN-67008 (C.F. Lynch), N01-CN-67010 (W. Cozen), N02-CP-19114 (D. Camann) and the Intramural Research Program of the NIH/National Cancer Institute.

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doi:10.1158/1055-9965.EPI-05-0556

sample, and a drinking water sample. Participants provided (or refused) written, informed consent separately for each data collection component and were given a cash token of appreciation.

The computer-assisted interview included a detailed history of pesticide use in residences occupied for ≥2 years since 1970. For each home, the interviewer recorded the years moved in and out and asked about pesticide treatment for eight specific types of insects, using showcards to increase respondent attention and accuracy: lawn insects; insects on outdoor plants and trees (here referred to as ''garden''); insects on indoor plants; and each of several types of insects treated in or around the home, excluding the lawn and garden (crawling insects, flying insects, fleas/ticks on pets, fleas/ticks in the home, and termites). We did not ask subjects to name the specific product used because people typically have trouble recalling this information (4). For each pest type, the respondent was asked whether pesticides were used, who applied the product, the frequency, and the form (e.g., spray and powder). For termites, the interviewer also asked which years the treatments occurred or, if the respondent could not remember, whether they occurred before or after 1988 (when the termiticide chlordane was banned in the United States). Unless otherwise noted, use of insecticides includes applications by the respondent, a professional, or someone else.

Of 2,248 potentially eligible cases, 320 (14%) died before they could be interviewed, 127 (6%) could not be found, 16 (1%) had moved away, and 57 (3%) had physician refusals. We attempted to contact the remaining 1,728, of whom 1,321 (76%) participated. Of the 2,409 potentially eligible controls, 28 (1%) died before they could be interviewed, 311 (13%) were unlocatable, and 24 (1%) had moved away. We attempted to contact the other 2,046, of whom 1,057 (52%) participated. Participation was higher for some subgroups [Iowa cases (81%) and controls (63%), female cases (79%), Caucasian cases (89%) and controls (60%), and follicular lymphoma cases (79%)].

We asked each interviewed subject for permission to collect a dust sample, and 93% of cases and 95% of controls agreed. These 1,233 cases and 1,004 controls were screened for eligibility for dust sampling. Subjects were eligible (695 cases and 521 controls) if they had used their vacuum cleaner within the past year and had owned at least half of their carpets or rugs for ≥5 years. The interviewer removed the used bag from the subject's vacuum, placed it in an insulated shipping box, and mailed the box overnight to Southwest Research Institute (San Antonio, TX). The median length of residence in homes with carpet dust samples was 20 years for both cases and controls.

Dust Samples: Laboratory Analysis and Data Imputation. Portions of dust from each vacuum cleaner bag were passed through a 100-mesh sieve to remove large particles such as human hair. The fine fraction (<150 μm) was aliquoted and frozen. Samples were grouped into batches of 13 to 15 for extraction and analysis, each batch containing at least four cases and four controls. Laboratory personnel were blinded to case-control status. Samples from 682 cases and 513 controls were analyzed; the remainder was lost in shipping or laboratory accidents, arrived at the laboratory with missing labels, or had insufficient dust for analysis.

Technicians spiked 2-g aliquots of dust with appropriate surrogates and did a ''neutrals'' extraction procedure (5). Extracts were analyzed using gas chromatography/mass spectrometry in selected ion monitoring mode; analyte amounts were quantified using the internal standard method. Eighteen insecticides were measured (aldrin, dieldrin, dicofol, α-chlordane, γ-chlordane, DDE, DDT, heptachlor, lindane, methoxychlor, bendiocarb, carbaryl, propoxur, chlorpyrifos, diazinon, malathion, *cis*-permethrin, and *trans*-permethrin). Usual detection limits ranged from 20.8 to 123 ng/g of dust. Changes in analytic procedures during the study resulted in there being two different usual detection limits for some insecticides (methoxychlor, carbaryl, chlorpyrifos, diazinon, malathion, *cis*-permethrin, and *trans*-permethrin). Dust samples weighing <2 g had detection limits that were higher than the usual detection limits.

Lab spikes of 27 dust samples showed that all insecticides were efficiently extracted, with recovery means ranging from 93% to 117% and recovery SDs from 10% to 30%, except for carbaryl (144 ± 54%), DDT (130 ± 26%), methoxychlor (140 ± 27%), and *trans*-permethrin (135 ± 31%). Reported levels in dust were not adjusted for spike recoveries. Analysis of lab splits of 27 dust samples (unblinded) showed close agreement between the regular sample and the split. The measurements for 85% of the 166 detection pairs agreed within 20%, and 98% agreed within 40%. Confirmation analyses done by full-scan gas chromatography/mass spectrometry on 55 samples verified the selected ion monitoring results, indicating that the analytes had been properly identified.

The laboratory measurements contained missing or ''interval-measured'' data, mainly when the concentration was below the gas chromatography/mass spectrometry detection limit but also when the sample contained interfering compounds (i.e., compounds that coeluted with the target analyte). We used an imputation procedure to assign values to both types of missing data for each insecticide that was detected in at least 10% of the samples (α-chlordane, γ-chlordane, DDE, DDT, methoxychlor, carbaryl, propoxur, chlorpyrifos, diazinon, *cis*-permethrin, and *trans*-permethrin). The imputation procedure, described in Colt et al. (5) and Lubin et al. (6), assigns a value for each missing measurement by selecting from the assumed distribution using maximum likelihood parameter estimates. Analytes with relatively high occurrences of interferences were methoxychlor (37% of samples), carbaryl (34%), DDT (16%), *cis*-permethrin and *trans*-permethrin (11%), and propoxur (10%); the others had no >2% of the values imputed due to interferences.

Data Analysis. We estimated the relative risk of developing NHL from reported use of pesticides and from residues in house dust by deriving adjusted odds ratios (OR) and 95% confidence intervals (95% CI) from multiple logistic regression models. For analyses of several histologic types, we used polytomous regression. Regression models included study center, sex, education (<12, 12-15, ≥16 years), age (<35, 35-44, 45-54, 55-64, and ≥65 years), and race (Caucasian, African American, other). Computations were done using SAS for Windows, version 8.2.

To estimate risk for treatment of each insect type, we estimated the total number of treatments across residences and grouped people accordingly. The reference group was composed of individuals who never treated for that insect type. [We attempted to define a single reference group composed of people who never treated for any insect, but too few subjects (45 cases and 33 controls) met this criterion.] We also aggregated treatments across all insect types to derive the total number of insecticide applications and estimated risk using a reference of individuals with <10 treatments.

For each insect type, there were people who could not recall whether one or more of their homes had been treated but knew that the others had not been. These subjects were included in the risk model in a separate category called ''no/unknown.'' We also encountered people who treated for an insect type in a given home but could not remember how often. To estimate the total number of treatments for these individuals, we simply summed the treatments across the homes for which such information was known. We conducted a sensitivity analysis excluding people with incomplete information on the number of treatments, and the risk estimates did not change appreciably for any insect type.

To estimate risk based on carpet dust residues, we slightly modified the approach used in our previous work on organochlorine compounds in carpet dust (3). As before, we defined a reference group of individuals whose measured or imputed concentration was below the usual detection limit. For analytes whose detection limit changed due to modifications in laboratory procedures, we used the higher of the two detection limits for this purpose. Here, individuals with detectable levels of an analyte were grouped into quartiles (previous work used tertiles) based on the control distribution, and tests of trend were done using natural log–transformed continuous variables (trend tests were categorical in previous work). We used log-transformed continuous variables to test for trend because the insecticide measurements were lognormally distributed, with wide concentration ranges in the uppermost categories.

Results

Characteristics of the study population are given elsewhere (7). Participants were predominantly elderly (60% of cases and 66% of controls were ages 55-74 years) and White (85% of cases and 80% of controls). Cases and controls were similar in terms of years of education. Both cases and controls had lived in three residences since 1970, on average, and most (76% of cases and 73% of controls) lived in single-family homes at the time of diagnosis or selection.

Use of insecticides on all insects combined was not associated with NHL risk, regardless of the number of applications (Table 1) or the years of use (data not shown). There was a statistically significant, 30% increase in risk among people whose home(s) had been treated for termites. Five or more termite treatments conferred a 50% nonsignificant excess risk, but there was no further increase with more treatments. Risk was similarly elevated among people who ever applied termiticides themselves (OR, 1.3; 95% CI, 0.6-2.6; 20 cases and 15 controls) and those who used an exterminator (OR, 1.2; 95% CI, 0.9-1.6; 205 cases and 164 controls; data not shown). There were no associations for any other insect type, regardless of the number of treatments (Table 1); the number of years of treatment; whether treatments occurred in the 1970s, 1980s, or 1990s; or who applied the insecticides (data not shown).

For most insect types, there were a large number of people in the ''no/unknown'' category (mixture of ''did not treat'' and ''don't know'' for different homes). Estimated risks were elevated in this category for many of the insect types, significantly so for garden insects (OR, 1.3; 95% CI, 1.0-1.7; 218 cases and 129 controls) and fleas/ticks in the home (OR, 1.7; 95% CI, 1.3-2.3; 168 cases and 82 controls; data not shown). We conducted a sensitivity analysis in which we included all of the people in the ''no/unknown'' category first in the reference group and then in the exposed group. There were no notable changes in risk estimates for any insect type, except that treatment of fleas in the home was associated with a small but significant increase in risk (OR, 1.2; 95% CI, 1.0-1.5) under the second scenario.

Termite treatment was associated with modestly, although not significantly, elevated risk in all sites except Seattle, in all races and sexes, and for both respondent and professional applications (Table 2). Risk was elevated only if treatments occurred before 1988, when chlordane-containing termiticides were banned.

We examined flea foggers (commonly known as ''flea bombs'') in detail because of their high potential for human exposure and found no elevation in risk (OR, 1.1; 95% CI, 0.9-1.4; 263 cases and 195 controls; data not shown). People who used flea bombs for <5 years were not at increased risk (OR, 1.1; 95% CI, 0.8-1.4; 147 cases and 109 controls) nor were those who used flea bombs for 5 to 9 years (OR, 1.1; 95% CI, 0.7-1.5; 71 cases and 59 controls). However, ≥10 years of use was associated with a 50% excess risk (95% CI, 0.9-2.5; 45 cases and 27 controls). There was no association with the number of times flea bombs were used (for ≥75 applications; OR, 1.2; 95% CI, 0.7-2.2; 25 cases and 19 controls).

Table 1. NHL risk according to treatment for insects

No. uses	No. cases/controls*	OR (95% CI)†
All insects		
0-9	169/122	1.0
10-99	457/392	0.8 (0.6-1.1)
100-199	290/245	0.9 (0.6-1.2)
200-299	174/122	1.1 (0.8-1.5)
300-399	91/79	0.9 (0.6-1.3)
400-499	50/41	0.9 (0.6-1.5)
≥500	50/45	0.8 (0.5-1.4)
Lawn insects		
Never	743/612	1.0
Ever	343/285	0.9 (0.8-1.2)
1-9	104/111	0.7 (0.5-1.0)
10-49	122/86	1.1 (0.8-1.5)
50-99	58/45	1.0 (0.7-1.5)
≥100	57/41	1.1 (0.7-1.7)
Garden insects		
Never	566/468	1.0
Ever	536/460	1.0 (0.8-1.2)
1-9	149/127	1.0 (0.7-1.3)
10-49	201/160	1.0 (0.8-1.3)
50-99	73/73	0.8 (0.6-1.2)
100-149	57/53	0.9 (0.6-1.3)
≥150	56/47	1.1 (0.7-1.7)
Indoor plant insects		
Never	1,003/818	1.0
Ever	143/134	0.9 (0.7-1.2)
1-9	67/61	0.9 (0.6-1.3)
10-49	36/39	0.8 (0.5-1.2)
≥50	37/31	1.0 (0.6-1.7)
Crawling insects		
Never	297/220	1.0
Ever	973/807	0.9 (0.7-1.1)
1-9	275/231	0.8 (0.6-1.1)
10-49	331/286	0.8 (0.6-1.1)
50-99	151/119	0.9 (0.7-1.2)
100-149	100/89	0.8 (0.6-1.2)
≥150	112/74	1.2 (0.8-1.8)
Flying insects		
Never	530/413	1.0
Ever	677/575	0.9 (0.8-1.1)
1-9	214/194	0.9 (0.7-1.1)
10-49	226/171	1.0 (0.8-1.3)
50-99	99/75	1.0 (0.7-1.4)
100-149	73/56	1.0 (0.7-1.5)
≥150	62/76	0.7 (0.5-1.0
Fleas/ticks on pets		
Never	452/378	1.0
Ever	777/621	1.0 (0.8-1.2)
1-9	191/178	0.8 (0.6-1.0)
10-49	284/192	1.2 (0.9-1.5)
50-99	141/113	1.0 (0.7-1.3)
100-149	94/85	0.9 (0.6-1.2)
≥150	62/48	1.2 (0.8-1.8)
Fleas/ticks in home		
Never	722/641	1.0
Ever	430/334	1.1 (0.9-1.3)
1-9	244/181	1.1 (0.9-1.4)
10-49	115/96	1.0 (0.8-1.4)
≥50	69/56	1.1 (0.8-1.6)
Termites		
Never	806/674	1.0
Ever	333/254	1.3 (1.0-1.6)
1	116/88	1.3 (1.0-1.8)
2	53/43	1.3 (0.8-2.0)
3-4	30/22	1.3 (0.7-2.3)
≥5	38/25	1.5 (0.9-2.6)

*Cases and controls with a combination of ''no'' and ''don't know'' for different homes in response to the question ''Was this home ever treated for [*insect type*]?'' are excluded from the table. Cases and controls who treated for an insect type but provided no information on the treatment frequency for any of their homes are included in the ''ever/never'' risk estimates but excluded from analyses based on the number of uses.

†Adjusted for site, sex, age, education, and race.

Among respondents with carpet dust samples, we observed a significant trend of increasing risk with increasing levels of α-chlordane (P_{trend} = 0.04) and a marginally significant trend for γ-chlordane (P_{trend} = 0.06; Table 3). There was a 40% elevation in the highest exposure categories of both α-chlordane and γ-chlordane. We observed a general pattern of increasing risk for propoxur and decreasing risk for diazinon, but the trends were not statistically significant.

We combined the information on termiticide use with γ-chlordane measurements in dust to isolate two groups of people in whose exposure status we were most confident. We defined a reference group whose homes were never treated for termites and whose dust had no γ-chlordane detected (Table 4). Compared with them, participants reporting three or more termiticide treatments and with γ-chlordane levels above the median (based on the distribution of detected values among controls) had a statistically significant, 2.8-fold risk of NHL. Restricting the highest exposed category to γ-chlordane measurements above the 75th percentile (20 cases and 4 controls), the OR increased to 4.9 (95% CI, 1.6-14.9; data not shown). Patterns were similar for α-chlordane, with a 3.5-fold risk among people with three or more termite treatments and above-median α-chlordane levels, rising to 3.9 (95% CI, 1.3-12.0; 16 cases and 4 controls; data not shown) when the highest exposed category was defined by the 75th percentile. These findings were consistent for Los Angeles and Iowa, where termite treatments and chlordane detections were more prevalent, but could not be evaluated separately for Detroit and Seattle because of small numbers.

We examined termiticide use before 1988 and γ-chlordane (the more frequently detected isomer) levels above the median among various subpopulations (Table 5). Elevations in risk were most pronounced in the youngest and oldest age groups, in Iowa, among non–African Americans, and for diffuse and T-cell lymphomas. Elevated γ-chlordane increased risk among men but not women. Among participants reporting a family history of NHL, there was a fourfold risk of NHL for termite treatment before 1988 and a 50% excess for elevated γ-chlordane levels, but these estimates are unstable because of small numbers.

Discussion

We found a positive association between NHL risk and treatment of homes for termites, with modest elevations in three of the four study centers, both sexes, and all racial groups. Treatment after the 1988 chlordane ban did not increase risk, although this could be related to latency effects rather than a change in termiticide formulations. There was a significant trend of increasing risk with increasing levels of α-chlordane residues in carpet dust (P_{trend} = 0.04) and a marginally significant trend for γ-chlordane (P_{trend} = 0.06).

Chlordane termiticides contain many compounds, predominantly α-chlordane and γ-chlordane but also including heptachlor; *cis*-nonachlor and *trans*-nonachlor; α-chlordene, β-chlordene, and γ-chlordene; and others. Chlordane was first used in the United States in 1948 and was once widely used on crops. In 1978, all uses were suspended except for subterranean termite control and dipping of nonfood plants. From 1983 to 1988, its only approved use was for termite control. Chlordane was banned because of concerns over cancer risk, build-up in body fat, persistence in the environment, and danger to wildlife (8). Chlordane has been detected in the indoor air of homes 15 years after termite treatment (9).

NHL is a cancer of the immune system, and it has been postulated that exposures affecting the immune system may increase NHL risk. There are limited data to indicate that chlordane and its constituents have effects on the immune

Table 3. NHL risk according to insecticide levels measured in carpet dust

Insecticide	ng/g in dust	Ca/Co	OR (95% CI)*	P_{trend} †
γ-Chlordane	Not detected	350/268	1.0	0.06
	20.9-35.6	77/61	1.0 (0.7-1.4)	
	35.7-65.1	71/61	0.9 (0.6-1.4)	
	65.3-166	83/61	1.1 (0.8-1.6)	
	167-8,710	101/62	1.4 (0.9-2.0)	
α-Chlordane	Not detected	409/317	1.0	0.04
	20.8-34.0	54/49	0.9 (0.6-1.3)	
	34.2-60.1	62/49	1.0 (0.7-1.5)	
	60.3-156	77/49	1.3 (0.9-2.0)	
	157-5,870	80/49	1.4 (0.9-2.1)	
Methoxychlor	Not detected	407/299	1.0	0.54
	62.5-119	69/54	1.0 (0.7-1.5)	
	120-213	58/53	0.9 (0.6-1.3)	
	216-595	83/54	1.2 (0.8-1.7)	
	605-100,000	65/53	1.0 (0.7-1.5)	
Propoxur	Not detected	145/119	1.0	0.16
	21.2-48.2	112/98	0.9 (0.6-1.3)	
	48.3-97.1	136/99	1.1 (0.8-1.6)	
	97.2-287	146/98	1.3 (0.9-1.9)	
	288-38,200	143/99	1.3 (0.9-1.9)	
Carbaryl	Not detected	466/333	1.0	0.51
	125-216	49/46	0.7 (0.5-1.1)	
	218-829	82/44	1.3 (0.9-2.0)	
	835-1,910	51/45	0.8 (0.5-1.2)	
	1,940-223,000	34/45	0.5 (0.3-0.9)	
Chlorpyrifos	Not detected	243/165	1.0	0.20
	41.8-91.7	94/87	0.7 (0.5-1.0)	
	92.8-247	151/87	1.1 (0.8-1.6)	
	249-796	101/87	0.8 (0.5-1.1)	
	799-38,200	93/87	0.7 (0.5-1.0)	
Diazinon	Not detected	466/314	1.0	0.12
	46.5-71.3	59/49	0.8 (0.5-1.2)	
	71.4-158	70/50	0.9 (0.6-1.3)	
	161-403	38/50	0.5 (0.3-0.8)	
	407-197,000	49/50	0.7 (0.4-1.1)	
cis-Permethrin	Not detected	203/142	1.0	0.88
	76.3-270	107/93	0.8 (0.5-1.1)	
	272-888	118/92	0.9 (0.7-1.3)	
	906-4,120	140/93	1.1 (0.8-1.5)	
	4,140-240,000	114/93	0.9 (0.6-1.3)	
trans-Permethrin	Not detected	199/135	1.0	0.86
	123-517	115/94	0.8 (0.6-1.2)	
	520-1,540	113/95	0.8 (0.6-1.2)	
	1,550-6,810	132/94	1.0 (0.7-1.4)	
	6,830-328,000	123/95	0.9 (0.6-1.3)	

*Adjusted for site, sex, age, education, and race. Referent group for categorical analyses is "not detected."
†Natural log-transformed continuous variable.

Table 2. NHL risk according to ever treatment for termites

Subgroup	Ca/Co	OR (95% CI)*
Study site		
Detroit	17/9	1.5 (0.6-3.6)
Iowa	70/44	1.3 (0.8-2.0)
Los Angeles	204/157	1.3 (0.9-1.9)
Seattle	42/44	0.8 (0.5-1.3)
Sex		
Men	176/136	1.3 (0.9-1.7)
Women	157/118	1.3 (0.9-1.8)
Race		
African American	37/63	1.2 (0.6-2.4)
Caucasian	264/173	1.3 (1.0-1.6)
Other	32/18	1.3 (0.6-3.1)
Who applied		
Respondent applied	20/15	1.3 (0.6-2.6)
Professional applied	205/164	1.3 (0.9-1.6)
When applied		
Applied before 1988	220/162†	1.3 (1.0-1.7)
Applied only after 1988	46/43†	1.0 (0.7-1.6)

*Adjusted for site, sex, age, education, and race.
†Termiticide users were excluded if we could not determine whether the home was treated before 1988.

Table 4. Risk of NHL according to termiticide applications and chlordane levels in dust

Isomer	Concentration	No termiticide applications			1-2 termiticide applications			≥3 termiticide applications		
		Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
γ-Chlordane	Not detected	262	214	1.0	20	15	1.3 (0.6-2.6)	12	9	1.1 (0.5-2.7)
	≤ Median*	92	89	0.8 (0.6-1.2)	21	13	1.6 (0.7-3.3)	7	7	1.1 (0.4-3.2)
	> Median	81	48	1.5 (1.0-2.2)	41	34	1.3 (0.7-2.1)	26	9	2.8 (1.3-6.3)
α-Chlordane	Not detected	300	249	1.0	27	20	1.3 (0.7-2.4)	14	11	1.1 (0.5-2.5)
	≤ Median †	67	62	0.9 (0.6-1.3)	22	13	1.7 (0.8-3.5)	7	7	1.1 (0.4-3.2)
	> Median	68	40	1.5 (1.0-2.3)	33	29	1.2 (0.7-2.2)	24	7	3.5 (1.4-8.4)

NOTE: Table excludes 67 cases and 40 controls who had ''no/unknown'' termite treatment, and 53 cases and 35 controls who treated for termites but could not recall the number of times. Median concentrations of γ-chlordane and α-chlordane were based on all subjects, including those excluded from this table.
*Median detected γ-chlordane concentration among controls was 65.3 ng/g.
†Median detected α-chlordane concentration among controls was 60.1 ng/g.

system. In an experimental mouse model, Tryphonas et al. found that *cis*-nonachlor increased IgG levels, although chlordane itself had no effect (10). Both *cis*-nonachlor and *trans*-nonachlor led to an increased susceptibility of mice to bacterial infection, suggesting that the chemicals are immunosuppressing. In humans, exposure to chlordane was associated with decreased lymphocyte responsiveness and the frequent presence of autoantibodies (11). Additional research is needed to clarify the effects of chlordane on the immune system.

The epidemiologic literature on chlordane is mixed. There were no excess deaths from lymphatic and hematopoietic cancer in studies of the mortality experience of 800 chlordane manufacturing plant workers (12) or 16,124 pesticide applicators nor in the subset of pesticide applicators involved in termite control (13). A Canadian population-based case-control study found no association (14). However, three other population-based case-control studies reported elevated risk from self-reported occupational exposure to chlordane. In Iowa and Minnesota, risk was significantly elevated (OR, 1.7) among farmers who handled chlordane, particularly if they did not use protective equipment (OR, 2.2; ref. 15). Men reporting previous exposure to chlordane had a significant NHL excess (OR, 2.1) in Nebraska (16) and a nonsignificant excess (OR, 1.6) in Washington State (17). A pooled analysis (18) from studies in Nebraska (19), Iowa and Minnesota (15), and Kansas (20) found a nonsignificant excess (OR, 1.5).

Studies with biological samples have generally reported positive associations. In a hospital-based case-control study in

Table 5. NHL risk according to termite treatment and γ-chlordane levels in dust, by sex, age, site, race, education, farming status, family history of NHL, and histologic subtype

Subgroup	Treated for termites before 1988*		γ-Chlordane above median detected value in dust †	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Sex				
Men	119/89	1.3 (0.9-1.8)	104/60	1.5 (1.0-2.3)
Women	101/73	1.4 (0.9-2.0)	80/62	1.0 (0.7-1.6)
Age (y)				
<45	28/16	1.6 (0.7-3.3)	20/10	1.4 (0.5-3.6)
45-64	109/87	1.0 (0.7-1.4)	78/46	1.1 (0.7-1.8)
≥65	83/59	1.8 (1.2-2.7)	86/66	1.2 (0.8-1.9)
Study site				
Detroit	9/6	1.1 (0.4-3.3)	21/10	1.1 (0.5-2.7)
Iowa	56/29	1.6 (1.0-2.6)	57/29	1.8 (1.1-3.1)
Los Angeles	126/97	1.3 (0.9-2.0)	87/62	1.2 (0.7-2.2)
Seattle	29/30	0.8 (0.5-1.5)	19/21	0.8 (0.4-1.5)
Race				
African American	21/40	1.0 (0.5-2.2)	13/18	0.5 (0.2-1.5)
Caucasian	177/111	1.3 (1.0-1.8)	158/98	1.3 (0.9-1.8)
Other/UK	22/11	1.4 (0.5-3.7)	13/6	1.4 (0.4-5.6)
Education (y)				
<12	21/17	1.0 (0.4-2.4)	16/15	1.0 (0.4-2.6)
12-15	127/87	1.6 (1.1-2.2)	111/73	1.2 (0.9-1.8)
≥16	72/58	1.0 (0.7-1.6)	57/34	1.4 (0.8-2.4)
Farming status				
Never farmed ‡	209/154	1.3 (1.0-1.7)	165/111	1.2 (0.9-1.6)
Ever farmed ‡	9/7	0.8 (0.3-2.6)	18/11	1.9 (0.7-5.1)
Family history of NHL				
No	181/137	1.2 (0.9-1.6)	150/101	1.3 (0.9-1.8)
Yes§	9/2	4.3 (0.7-26.0)	5/2	1.5 (0.2-10.6)
Histologic subtype				
Follicular	41/162	1.1 (0.7-1.6)	42/122	1.2 (0.8-1.8)
Diffuse	74/162	1.5 (1.0-2.1)	58/122	1.4 (0.9-2.0)
T cell	13/162	1.5 (0.7-3.0)	12/122	1.9 (0.8-4.2)
Other	78/162	1.4 (1.0-1.9)	61/122	1.1 (0.8-1.7)
Unknown	14/162	0.8 (0.4-1.7)	11/122	2.0 (0.5-7.4)

*n = 1,321 cases and 1,057 controls interviewed; reference = never treated for termites.
†n = 682 cases and 513 controls with dust samples; reference = γ-chlordane not detected in dust.
‡Excludes two cases and one control with unknown farming status.
§Includes 11 cases and 6 controls reporting a family history of unspecified ''lymphoma.''

Sweden (27 cases), Hardell et al. (21) found a significant increase in NHL risk associated with postdiagnostic adipose tissue levels of six summed chlordane compounds (OR, 4.1). Hardell later reported that among subjects with high titers to EBV early antigen antibody, higher levels of chlordane-related compounds in blood were significantly associated with NHL risk (OR, 4.0; 67 cases; ref. 22). In a nested case-control study using adipose tissue samples collected randomly from cadavers and surgical patients (174 cases), higher levels of oxychlordane were significantly associated with NHL risk (P_{trend} = 0.0002; ref. 23). However, in a nested case-control study in Maryland (74 cases), no association was reported between prediagnostic serum levels of chlordane-related compounds and NHL risk (24).

In our study, we did not have biological measures of organochlorine metabolites for the overall study population, but we did measure them in plasma from 100 untreated cases and 100 controls. Although there was no consistent pattern of increasing risk by quartiles of chlordane metabolites, risk was elevated for oxychlordane (OR, 2.9; 95% CI, 0.6-13.2) and *trans*-nonachlor (OR, 2.0; 95% CI, 0.5-7.5) levels above the 95th percentile (25).

NHL comprises a large number of distinct diseases with different incidence patterns, clinical features, and etiology (26, 27). In our study, pre-1988 termiticide use and high chlordane residues in dust were each more strongly associated with diffuse large B-cell lymphoma and T-cell lymphoma than the other histologic subtypes. The interpretation of this finding is unclear. Cantor et al. (15) reported that use of cyclodiene insecticides (a group that includes chlordane) on livestock significantly increased the risk of diffuse NHL (OR, 2.2; 95% CI, 1.1-4.5); other studies of chlordane and NHL risk have not reported on histologic subtypes. The number of T-cell lymphoma cases in each exposed group was small (13 treated for termites before 1988; 12 had chlordane residues above the median). There is no a priori reason to expect any specific chemical agent to increase the risk of both B-cell lymphoma and T-cell lymphoma.

Our findings could overstate the association with NHL if cases systematically overreported, or controls underreported, termiticide use. We attempted to minimize recall bias by querying subjects about pesticide use home by home (rather than asking them to integrate pest treatment practices over their lifetimes) and using showcards to stimulate memory. That risk was elevated for only one insect type suggests that our findings are not attributable to recall bias. The similarity in proportions of case homes and control homes with ''unknown'' termite treatment (8%) provides further evidence against recall bias. Finally, the positive association for chlordane residues in dust, which supports the termite treatment finding, would not be influenced by recall bias.

The moderately elevated ORs for termite treatment and chlordane residues might actually understate the true risks, as there is ample opportunity for nondifferential misclassification of exposure. For example, people often move into homes that were previously treated for termites without their knowledge, and many people who did treat for termites may have subsequently replaced their carpets. When we isolated two groups of people in whose exposure status we were relatively confident (an unexposed group with no termite treatments and no measurable chlordane residues and an exposed group with three or more termite treatments and above-median chlordane levels), the exposed group had a 3- to 4-fold NHL risk.

We found no association between NHL risk and residential treatment for insects overall or for any individual insect type other than termites. There are few studies of residential insecticide use and adult lymphoma. Residential insecticide did not increase NHL risk among women in Nebraska (OR, 1.2; 95% CI, 0.8-1.8; ref. 28). Our findings do not corroborate those of a case-control study of women in New York State (excluding New York City and surrounding counties), in which the cumulative frequency of household pesticide use was positively associated with NHL risk (P_{trend} = 0.004), with a 60% nonsignificant excess in the highest exposure category (≥185 lifetime applications; ref. 29). Differences in study design could account for the discrepant findings. In New York, interviews were conducted over the telephone with the subject or, if deceased, the next-of-kin, most commonly children (ours were all in-person, direct interviews). Both studies asked about pesticide use by pest type, but the New York study did not ascertain this information home by home. Although the total number of pesticide applications in New York included herbicides and fungicides as well as insecticides and covered subjects' entire lifetimes, only 19% of controls exceeded 185 applications compared with 31% of the female controls in our study, suggesting that the New York controls might have underreported pesticide use, inflating the risk estimates. No association was found in New York for other pest categories. Findings were not reported separately for termites.

Elevated residues of insecticides other than DDE (3) and chlordane did not increase NHL risk. Because these other insecticides were commonly used in recent years, their levels were probably influenced more strongly by recent than past use. The literature on specific insecticides derives from their use in occupational settings. Diazinon and malathion use on farms were associated with significant, 2-fold elevations in risk in Nebraska (16) and 50%, nonsignificant excesses in Iowa and Minnesota (15). When these data were pooled with a similar study in Kansas, both insecticides had significantly increased NHL risk, although risks were largely attenuated when restricted to subjects providing direct interviews (30). A Canadian case-control study found a 70%, nonsignificant excess for diazinon and an 80%, significant excess for malathion (14). There was a significant 3-fold risk among a small number of chlorpyrifos users in the pooled study (30). Recently, the Agricultural Health Study cohort reported a nonsignificant NHL excess from cumulative exposure to chlorpyrifos but no relationship with frequency of use (31). Occupational use of carbaryl was associated with elevated NHL risk in Nebraska (16, 28); in Iowa and Minnesota (15), in data pooled from these two studies and a similar study in Kansas (32); and in Canada (14). A population-based case-control study in Sweden observed no excess risk from exposure to pyrethrins or pyrethroid insecticides (33).

The chief strength of our study is the detailed information from both a personal interview and carpet dust samples. Additional strengths are the population basis of the selection of subjects, the size of the study population, and the availability of data on other factors that might relate to NHL risk or to insecticide use. The chief weakness is the loss of information from death, inability to locate, refusal, or absence of eligible carpets. Bias could occur if, on balance, these factors are strongly related to disease status and to pest treatment practices or pesticide levels in dust. There is no way to evaluate this directly. However, in Iowa, where participation rates were highest, the associations for termite treatment and chlordane levels in dust were strongest. In addition, the findings for termite treatment were similar in those with and without carpet dust samples.

A shortcoming is our inability to account for dietary exposure to insecticides. The resulting misclassification of exposure is likely to be nondifferential, biasing risk estimates towards the null. Another factor that might lead to underestimates of risk is the absence of a truly unexposed reference group. Because many insecticides are used to treat a broad spectrum of pests, the reference group for each insect type likely includes people who treated for other types of insects using the same pesticides as those in the exposed group.

Moreover, we are all inadvertently exposed to pesticides applied in public buildings and outdoor areas. Finally, the *P*s for the dose-response trends for insecticide levels in dust are subject to uncertainty because they were based on a single imputation.

In conclusion, our study suggests that residential use of chlordane termiticides increases residents' NHL risk. Although the associations were not strong, they were consistent with an effect of treating homes for termites before the 1988 ban on chlordane use. The concurrent finding of elevated risk among participants with the highest levels of chlordane metabolites in plasma further supports this conclusion. We did not find associations for treatment of other insect types or for elevated residues of many other home and garden insecticides commonly used between 1970 and 2000. Although occupational use of many of these insecticides did increase NHL risk in other studies, the lack of an association in our study could be due to differences in exposure levels between occupational and residential users.

Acknowledgments

We thank C. Haines (Westat, Rockville, MD) for study coordination, L. Capece and S. Palladino (IMS, Silver Spring, MD) for computer support, K. Shea and C. Chorley (BBI-Biotech, Gaithersburg, MD) for biospecimen handling, and G. Tobias (National Cancer Institute, Rockville, MD) for research assistance.

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